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Ti(II)-Mediated domino cyclization of 2-functionalized 1-halo-2,n-enynes (n = 7, 8) to bicyclic compounds

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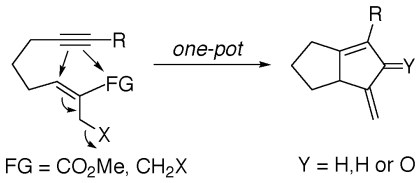

The reaction of 2-functionalized 1-halo-2,n-enynes with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl proceeded in a domino fashion to yield bicyclic compounds.

Ti(II)-Mediated domino cyclization of 2-functionalized 1-halo-2,n-enynes (n = 7, 8) to bicyclic compounds

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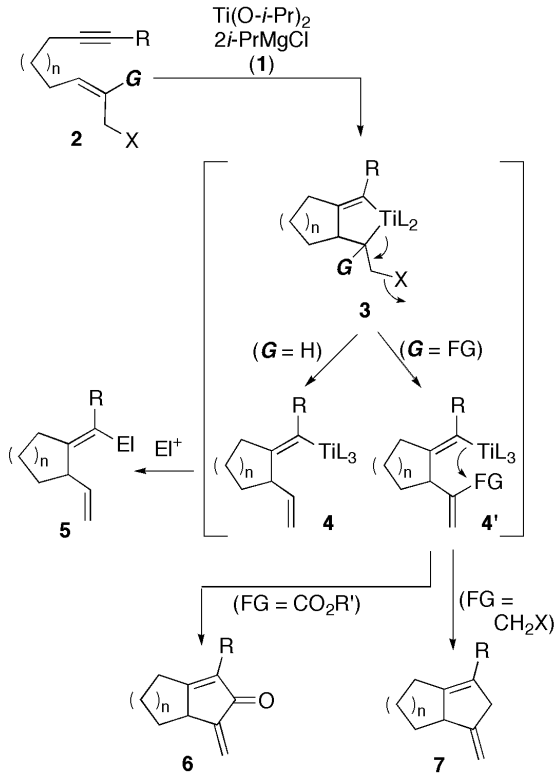
Abstract—The reaction of 2-functionalized 1-halo-2,n-enynes (n = 7 or 8) with a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, proceeded in a domino fashion to afford bicyclic compounds in good yields.

We have recently developed a divalent titanium reagent-mediated cyclization of 2,7- and 2,8-enyn-1-ol derivatives. Thus, the reaction of enyn-1-ol derivatives **2** (G = H) with Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**1**)[1] proceeded through β-elimination of the leaving group X from a titanacyclic intermediate **3** (G = H) to give alkenyltitanium compound **4** (Scheme 1).[2] The resulting alkenyltitaniums **4** could act as a nucleophile and reacted with various electrophiles to give **5**. With these results in hand, we thought that further intramolecular cyclization of the resulting alkenyltitaniums of the type **4** to bicyclic compounds might occur in a domino fashion[3] when the starting enynes have a functional group (FG), which can react with the alkenyltitanium moiety, as a substituent G at a C-2 position (Scheme 1). Herein reported is the realization of this idea by introducing -CO_2R' or -CH_2Cl as the FG at a C-2 position of 2,7- and 2,8-enyn-1-ol derivatives, which might be expected to produce the corresponding bicyclic products **6** and **7**, respectively.[4]

First, we investigated the **1**-mediated reaction of **2a**, which has a methoxycarbonyl group as the substituent G (Table 1). Thus, enynol derivative **2a** was treated with 1.4 equiv of **1** at –40 to –20 °C for 2 h and the mixture was quenched by addition of H_2O. However, the expected dienone **6a** was not produced but 29% of enone compound **8** was produced with 37% of the recovered **2a** (Table 1, entry 1).



Scheme 1. Plan for domino reaction.

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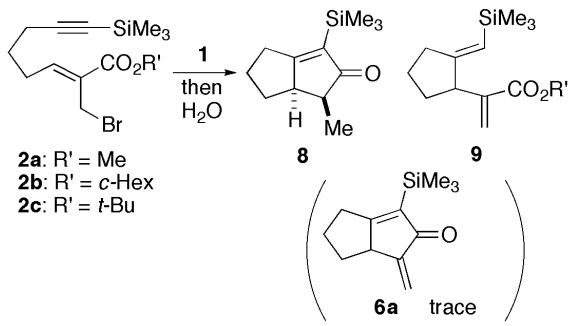
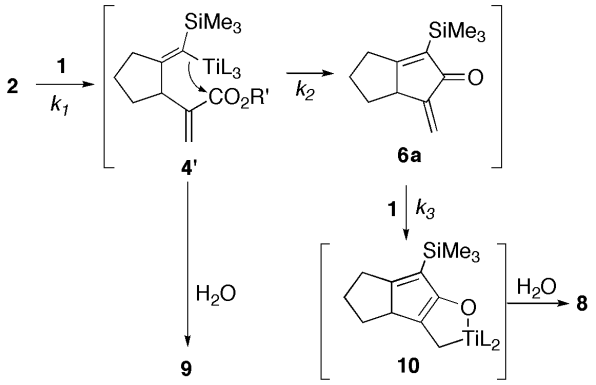
Table 1. Reactions of **5** with **1**.



entry	2	equiv of 1	yield, %		
			8	9	recovered 2
1	**2a**	1.4	29	trace	37
2	**2a**	2.3	84	trace	trace
3	**2b**	1.4	35	60	trace
4	**2c**	1.4	trace	93	trace

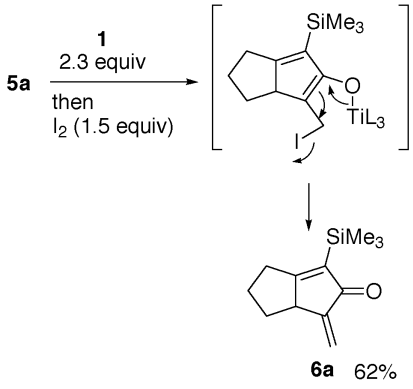
Therefore, we carried out the reaction using 2.3 equiv of **1** and found that the reaction provided **8** [diastereomeric ratio (d.r.) = 95:5] in 84% yield (Table 1, entry 2).[5,6] Enynes **2** having a more sterically demanding ester group reacted smoothly with 1.4 equiv of **1** but afforded mono-cyclic compounds **9**[5] as a major product (entries 3 and 4).

The results can be explained by assuming that the reaction of **2a** with **1** provided dienone **6a** *via* **4'a** as expected, however, the resulting **6a** further reacted with **1** fast to afford the corresponding oxatitanacyclic compound **10**, hydrolysis of which gave **8** (the order of reaction rates: k_2, $k_3 > k_1$) (Scheme 2). Introduction of cyclohexyl group into an ester moiety relatively decreased the reaction rate from the corresponding **4'** to **6a** (k_2) and, therefore, the reaction provided a mixture of **8** and **9** (k_1, $k_3 > k_2$). *t*-Bu group may be so bulky that intramolecular acyl substitution reaction of the corresponding **4'** could not undergo.



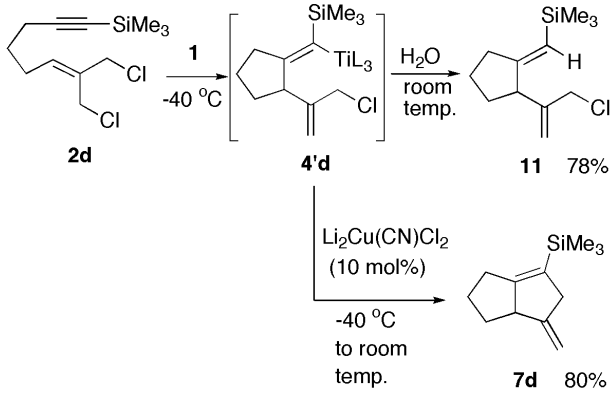
Scheme 2. Possible explanation for formation of **8** and **9**.

The presence of an intermediate **10** was confirmed by iodolysis of the reaction mixture derived from **2a** and 2.3 equiv of **1** (Scheme 3): The reaction mixture was treated with I_2 to give **6a** in 62% yield.[5] Thus, Ti(II)-mediated domino cyclization could provide bicyclic compounds **6a** and **8** having a cyclopentene and methylenecyclopenetene structures, respectively, from the acyclic enyne starting compound.



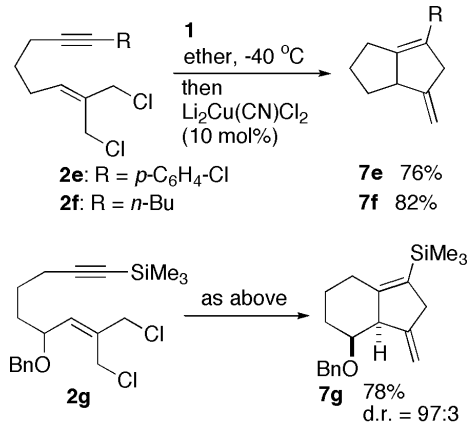
Scheme 3. Formation of **6a** by the reaction of **10** with I_2.

Next, we prepared enyne **2d** as a substrate which has a chloromethyl moiety as the substituent G at the C-2 position, expecting that the corresponding titanium compound **4'd** could undergo intramolecular allylic substitution giving **7d** (Scheme 4). Treatment of **2d** with 1.2 equiv of **1**, however, resulted in production of mono-cyclic compound **11** after hydrolysis. The results indicate that generated alkenyltitanium **4'd** could not undergo allylic substitution. It was found that addition of a catalytic amount of $Li_2Cu(CN)Cl_2$ to the reaction mixture of **4'd** could effect intramolecular allylic substitution to produce 1,2-annulated fuluvenes **7d** in 80% yield.[5,7]



Scheme 4. Reaction of **2d** with **1** and the following Cu-catalyzed cyclization.

Under similar reaction conditions, analogous compounds **2e**-**2g** reacted smoothly with a divalent titanium reagent **1** and then $Li_2Cu(CN)Cl_2$ catalyst to afford the corresponding 1,2-annulated fuluvenes **7e**-**7g**, respectively, in good yield (Scheme 5). High 1,2-diastereoselectivity was observed in the reaction of **2g**.[6]



Scheme 5. Domino Ti(II)-mediated and Cu-catalyzed bicyclization reactions.

Scheme 6 illustrates preparation of the substrates **2** for the present cyclization reactions. Thus, compounds **2a-c** were synthesized Baylis-Hillman reaction[8] of acrylic esters with 6-trimethylsilylhex-5-ynal (**12**) followed by bromination of the resulting alcohols, where the bromination reaction proceeded stereoselctively to yield the corresponding bromoesters as a *Z* isomer. While, compounds **2d-f** were prepared from the known 5-bromomethylene-2,2-dimethyl-[1,3]dioxane (**13**)[9] by Suzuki-Miyaura coupling reaction and the following cleavage of ketal and chlorination of the resulting diols.[10] Compound **2g** was obtained *via* the lithiation of **13** and the reaction with aldehyde **12**.

In summary, we have demonstrated that a divalent titanium reagent could effectively cyclize 2-functionalized 2,7- and 2,8-enyn-1-ol derivatives in a domino fashion to provide bicyclic compounds. The synthetic application of the present method is now underway in our laboratory.

Acknowledgments

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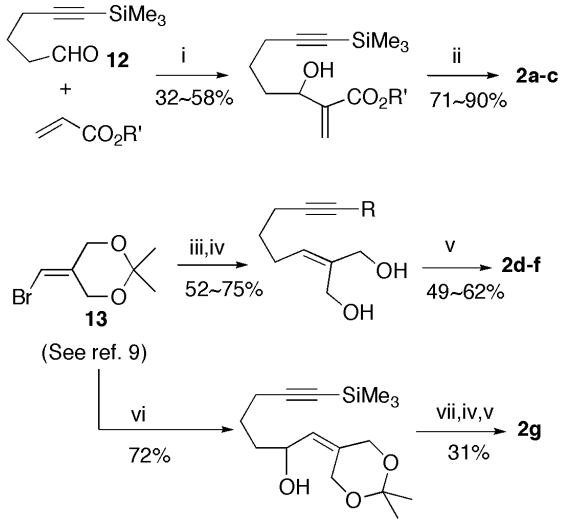

Scheme 6. Preparation of 5. *Conditions*: (i) PhOH (0.2 eq.), *n*-Bu_3P (0.2 eq.), THF, 50 °C (ii) NBS (2 eq.), Me_2S (2 eq.), CH_2Cl_2, rt., 12 h (iii) R-C≡CCH_2CH=CH_2 (1.5 eq.), 9-BBN (1.5 eq.), THF, rt., 12 h then **13**, cat. $PdCl_2$(dppf) (0.05 eq.), K_3PO_4 (3 eq), reflux, 2h (iv) *p*-TsOH (0.05 eq.), THF-H_2O, rt., 2.5 h (v) MsCl (2.5 eq.), Et_3N (5.4 eq.), CH_2Cl_2, rt., 12 h (vi) *t*-BuLi (2 eq.), ether, -78 °C then **12** (vii) BnBr (1.2 eq.), NaH (1.4 eq.), THF, rt., 12 h.

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5. Compound **8**: To a solution of **2a** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (2.3 mmol) in ether (10 mL) was added *i*-PrMgCl (4.6 mmol, 0.97 M in ether) at -40 ^{o}C and the mixture was stirred for 2 h at this temperature. After addition of aqueous 1M HCl, usual extractive work-up was followed; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39-2.70 (m, 3H), 2.18 (dt, *J* = 12, 6.6 Hz, 1H), 1.83-2.11 (m, 4H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.18 (s, 9H). Compound **9c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (br s, 1H0, 5.43 (br s, 1H), 5.20 (q, *J* = 2.1 Hz, 1H), 3.36-3.43 (m, 1H), 2.33-2.46 (m, 2H), 1.40-1.97 (m, 4H), 1.47 (s, 9H), 0.08 (s, 9H). Compound **6a**: To the reaction mixture derived from **2a** (1.0 mmol) and **1** (2.3 mmol) prepared above was added a solution of I_2 (2.3 mmol) in ether at –20 ^{o}C. After addition of aqueous 1M HCl, usual extractive work-up was followed; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (br s, 1H), 5.26 (br s, 1H), 3.27-3.37 (m, 1H), 2.50-2.75 (m, 2H), 1.90-2.25 (m, 2H), 1.08-1.30 (m, 2H), 0.21 (s, 9H). Compound **7d**: To a solution of **2d** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (1.2 mmol) in ether (10 mL) was added *i*-PrMgCl (2.4 mmol, 0.97 M in ether) at –40 ^{o}C and the mixture was striied for 3 h at –40 ^{o}C. To the mixture was added $Li_2Cu(CN)Cl_2$ (0.1 mmol, 1.0 M in THF) and the mixture was gradually warmed to room temperature over 2 h. After addition of water (0.3 mL), NaF (1 g) and Celite (1 g), the mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by column chromatography on silica gel; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 and 4.75 (2 br s, each 1H), 3.37-3.52 (m, 2H), 3.16 (d, *J* = 18.6 Hz, 1H), 2.16-2.25 (m, 2H), 1.90-2.05 (m, 3H), 1.08-1.25 (m, 1H), 0.08 (s, 9H). Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (br s, 2H), 5.05 (s, 1H), 4.04 and 3.99 (2d, each *J* = 12.6 Hz, each 1H), 3.26 (t, *J* =6.3 Hz, 1H), 2.14-2.54 (m, 2H), 1.51-2.03 (m, 4H), 0.08 (s, 9H).
6. Stereochemistries of compounds **8** and **7g** were determined by ^{1}H-^{1}H cosy and noesy experiments. Explanation of these stereoselectivities must await further study.
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10. Although bromination of the intermediate diol was carried out, the resulting dibromides were relatively unstable to be stored.